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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	18.08.2004
Applicant's or agent's file reference 21298	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/03742	10.04.2003	21.06.2002

Applicant
ROCHE VITAMINS AG et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	de Haas, B Tel. +31 70 340-4738

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 21298	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/03742	International filing date *(day/month/year)* 10.04.2003	Priority date *(day/month/year)* 21.06.2002
International Patent Classification (IPC) or both national classification and IPC C12P23/00		
Applicant ROCHE VITAMINS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23.12.2003	18.08.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Smalt, R Telephone No. +31 70 340-4275

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/03742

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-7 as originally filed

Claims, Numbers

1-12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-12
Industrial applicability (IA)	Yes:	Claims	1-12
	No:	Claims	

2. Citations and explanations

see separate sheet

1. The following **documents** (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: WO 96 09393 A (REYNOLDS TECHNOLOGIES INC ;BIOSOURCE TECH INC (US); HANLEY KATHLEE) 28 March 1996 (1996-03-28)

D2: DATABASE WPI Section Ch, Week 200346 Derwent Publications Ltd., London, GB; Class D16, AN 2003-485780 XP002250540 & JP 2002 300896 A (TOYOTA JIDOSHA KK), 15 October 2002 (2002-10-15)

D3: BROWN G R ET AL: 'Phenoxypropylamines: a new series of squalene synthase inhibitors.' JOURNAL OF MEDICINAL CHEMISTRY. UNITED STATES 13 OCT 1995, vol. 38, no. 21, 13 October 1995 (1995-10-13), pages 4157-4160, XP002250539 ISSN: 0022-2623 cited in the application

D4: WO 00 01650 A (DCV INC) 13 January 2000 (2000-01-13)

D5: ROBINSON G W ET AL: 'CONSERVATION BETWEEN HUMAN AND FUNGAL SQUALENE SYNTHETASES: SIMILATITIES IN STRUCTURE, FUNCTION, AND REGULATION' MOLECULAR AND CELLULAR BIOLOGY, WASHINGTON, DC, US, vol. 13, no. 5, 1 May 1993 (1993-05-01), pages 2706-2717, XP000604626 ISSN: 0270-7306

D6: US-A-5 182 208 (JOHNSON ERIC A ET AL) 26 January 1993 (1993-01-26) cited in the application

2. **Inventive step**

2.1 The application concerns the application of inhibitors of the sterol biosynthetic pathway in favour of biomass flow into the carotenoid pathway. D1 clearly describes the application of squalane synthase blockage by various means, including use of inhibitors, to direct the carbon flow to non-steroid isoprenoids, specifically carotenoids. Although the proposed application is not actually performed, and the process is therefore considered to be novel over the cited prior art, in the absence of any indication of problems in the execution of the proposed application, no inventive step in the sense of Art.33(3) PCT can be recognized for doing what was already suggested in clear terms.

2.2 D2 mentions the inhibition of squalene synthase to direct the carbon flow away from sterol synthesis and towards production of farnesol and geranylgeraniol. Since the latter is the first compound in the pathway dedicated to non-steroidal isoprenoids, and squalene synthase is the first enzyme in the pathway dedicated to synthesis steroidal isoprenoids, it is obvious that application of this system in an organism capable of

producing carotenoids would produce higher yields of that compound. Again, no inventive step can be recognized in the sense of Art.33(3) PCT.

2.3 The dependent claims contribute a specific organism used in the carotenoid synthesis, and in other claims specific inhibitors used for the process, and particular culture conditions. The use of *Xanthophyllomyces dendrorhous/ Phaffia rhodozyma* for carotenoid biosynthesis is as good as standard procedure in the art, and the specific inhibitors used are known to inhibit squalene synthase, see e.g. D3, which is also cited in the application. The culture conditions are also standard conditions used for these kind of processes in the field.

2.4 It is known from D4-D6 that organisms completely deficient in squalene synthase activity require sterols to be added to the culture medium for survival. It should therefore come as no surprise that one has to be careful not to block squalene synthase activity completely, but rather to adjust the dosage of the inhibitor in a manner which will still allow growth, yet direct a significant amount of FPP towards the carotenoid pathway.

2.5 In summary, none of the present claims 1-12 meet the requirements of Art.33(3) PCT, as their subject-matter cannot be recognized to involve an inventive step in view of the cited prior art.